Risk Factors and Clinical Correlations of Urinary TGF-β1 in Children with Juvenile Idiopathic Arthritis and Early Kidney Fibrosis

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Summary

The course of juvenile idiopathic arthritis (JIA) is associated with a long-term inflammatory process and the use of non-steroidal anti-inflammatory drugs (NSAIDs), which can cause nephrotoxicity with fibrotic kidney damage in patients with JIA. Regardless of the etiology of joint damage, prolonged inflammation promotes the progression of fibrosis, and renal fibrosis is the final common stage of chronic kidney disease (CKD). Kidney biopsy, which is invasive, risky and underutilized, is generally considered the only clinical method to detect fibrosis. Over the past decade, some progress has been made in the search for minimally invasive biomarkers of early kidney fibrosis, with transforming growth factor-β1 (TGF-β1) playing a key role in the progression of kidney fibrosis, but the significance of TGF-β1 in children with JIA is unknown.

Material and Methods: 80 children with JIA were examined. Urinary TGF-β1 levels were determined using a TGF-β1 ELISA kit (DRG International, Inc., Germany, ELA-1864) according to the manufacturer’s instructions. Methods of variation statistics were used.

Results. The mean TGF-β1 level in our study was 20.26±16.34 (14.02, 12.5-17.98) pg/ml. Polyarthritis almost quadrupled the probability of pathological changes in TGF-β1. The overwhelming majority of children with elevated TGF-β1 suffered from polyarthritis (80.0 %) – one and a half times more often than those with relatively normal TGF-β1 concentration, p<0.04.

If the active stage of the disease lasted at least 4 years, the probability of elevated TGF-β1 increased more than sixfold. The tendency of significant nephrotoxic effect of prolonged active JIA was confirmed by the results of correlation analysis, according to which, in general, the duration of active JIA was directly related to the increase of TGF-β1 (p=0.38, p<0.001), and the duration of remission and the total duration of JIA had no significant correlation with it (p=−0.19 and p=0.18, respectively, p>0.05).

The direct dependence of elevated urinary TGF-β1 levels on clinical features such as polyarthritis and the duration of the active phase of JIA has been demonstrated. These clinical features in children with JIA can be considered as risk factors for the development of early renal fibrosis. Against the background of elevated TGF-β1, a reduced GFR according to the Hoek formula (≤90 ml/min/1.73 m²) was found in 95 % of cases, i.e. the estimates of the functional state of the kidneys obtained by two different methods were quite clearly the same. In the sample with TGF-β1<17.98 pg/ml, 22.76 % of children received immunobiologic therapy, while in the sample to increase TGF-β1 – only 14.76 %. Immunobiologic therapy reduced the risk of increasing this urinary marker by 5.5 times.

Conclusions. Elevated levels of the TGF-β1 biomarker were found in 25 % of children with JIA. An association of early renal fibrosis with duration of active phase of JIA ≥ 4 years, increased ESR, polyarthritis, arterial hypertension, and dental caries was observed. Elevated urinary TGF-β1 levels are associated with reduced eGFR and are observed in almost all children with eGFR<90 ml/min/1.73 m², confirming the importance of early renal fibrosis in the development of renal dysfunction.

Key words: Juvenile Idiopathic Arthritis; Kidneys; Children; Fibrosis Marker; TGF-β1; Immunobiologic Therapy; Kidney Damage.

Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group that includes several diseases with manifestations of arthritis of one or more joints lasting more than 6 weeks in children under 16 years of age of unknown etiology. JIA is a diagnosis of exclusion; it includes all forms of chronic childhood arthritis of unknown etiology. It is known that Juvenile Idiopathic Arthritis (JIA) develops due to a combination of genetic predisposition and environmental factors (probably infections). The course of JIA is associated with a long-term inflammatory process and long-term symptomatic use of NSAIDs, which not only help control the inflammatory symptoms of JIA, but also have nephrotoxic effects that can cause fibrotic kidney damage in patients with JIA [1, 2, 3].

The mechanism underlying progressive renal fibrosis is not fully understood, but it is generally accepted that inflammation is a key factor in its development,
induced as a protective response to injury in an attempt to eliminate the cause and promote organ recovery. Prolonged inflammation, regardless of the etiology of the injury, has been shown to contribute to the progression of fibrosis [4, 5], and renal fibrosis is the final common stage of chronic kidney disease [6, 7]. According to research [8], long-term inflammation in adult patients with rheumatoid arthritis plays an important role in the development of chronic kidney disease (CKD). At the same time, only one study has been published on the prevalence of CKD in children with JIA, in which 8% had arterial hypertension (AH) or proteinuria 65 months after disease onset [9].

Regardless of the underlying disease and the presence of provocative factors, tubulointerstitial fibrosis is a sign of progressive CKD [10], so its early detection and prognosis are of paramount importance. Currently, the only clinical tool to detect fibrosis is renal biopsy, which is invasive, risky, and not routinely used. However, over the past decade, some progress has been made in the search for minimally invasive biomarkers of early renal fibrosis [11], with transforming growth factor-β (TGF-β1) playing a key role in the progression of renal fibrosis [6].

Transforming growth factor beta (TGF-beta) is a protein (a member of the cytokine family) that controls proliferation, cell differentiation, and other functions in most cells. TGF-beta is a protein secreted by the cell into the extracellular environment. It exists in at least three isoforms: TGF-beta1, TGF-beta2, and TGF-beta3. TGF-beta is secreted by many cell types, including macrophages, in an inactive (latent) form in which it is coupled to two other polypeptides, latent TGF-beta binding protein (LTBP) and LAP. Serum proteases such as plasmin catalyze the release of active TGF-beta from the complex. This often occurs on the surface of macrophages where the latent TGF-beta complex is bound to the CD36 receptor by its ligand, thrombospondin-1 (TSP-1). Inflammatory stimuli that activate macrophages increase the release of active TGF-beta, leading to plasmin activation. Macrophages can also engulf IgG-bound latent TGF-beta complexes secreted by plasma cells by endocytosis and then release active TGF-beta into the interstitial fluid [5, 6, 11, 12, 13]. TGF-β1 manifests its profibrotic activity by stimulating fibroblast proliferation and synthesis of extracellular matrix – collagen types I, III and IV, proteoglycans, laminin and fibronectin [13].

In the available literature, we did not find any studies on TGF-β1 in JIA, but there are publications on the study of this marker in children with various kidney diseases. To date, researchers have described the TGF-β1 marker as an indicator of CKD progression [12], a marker of fibrosis [11], as well as an anti-inflammatory marker in bacterial kidney infections [14]. The polymorphism of the TGF-β1 gene is also being studied in various diseases. For example, a correlation between the +869T/C gene polymorphisms in TGF-β1 was found in adult patients with rheumatoid arthritis [15]. Serum TGF-β1 levels are being actively studied as a marker of synovial proliferation and progression in rheumatoid arthritis [16].

Based on the above, the hypothesis about the risk of early development of kidney fibrosis in children with JIA looks quite logical, and the need for timely correction of CKD actualizes the issue of non-invasive diagnosis of CKD using kidney biomarkers.

**The aim of the study** to determine the association between the level of TGF-β1 in urine as a marker of early kidney fibrosis in children with JIA, depending on the clinical course of the disease, the characteristics of comorbid factors, and the treatment scheme.

**Material and methods of the study**

A cross-sectional study was conducted in 2019-2020 on the basis of the cardio-rheumatology department of the Dnipro Regional Children’s Clinical Hospital. Informed consent was obtained from all patients. The study was conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the local ethics committee.

Inclusion criteria: children diagnosed with JIA according to EULAR criteria [2], informed parental consent to participate in the study. Exclusion criteria: congenital malformations of the urinary system, presence of acquired diseases of the urinary system in the history or at the time of the examination.

Medical records were analyzed to determine the child’s age at disease onset, duration and clinical features of JIA, and treatment regimen. Disease activity was assessed using the Juvenile Arthritis Disease Activity Score (JADAS-27) [2]. The clinical examination at the time of the study included an assessment of the children’s health status according to the Childhood Health Assessment Questionnaire (CHAQ) [17], general clinical (blood and urine tests), biochemical (serum creatinine and GFR according to the Schwartz formula, blood urea, C-reactive protein), immunoenzymometric (antinuclear antibodies, HLA B27 antigen) and immunologic (rheumatoid factor) methods. An ultrasound examination of the joints and kidneys was also performed. Blood serum creatinine levels were measured twice (first and third month of the study) using the Jaffe calorimetric kinetic method, and blood serum cystatin C levels were measured once in the third month of the study using a solid-phase enzyme immunoassay (Cystatin C-ELISA-BEST). A complete description of the study is presented in Flowchart 1.

The Hoek formula was used to determine the GFR by the level of cystatin C in the blood serum [18]:

\[
\text{GFR (ml/min/1.73 m}^2\text{)} = 80.35/\text{cystatin C (mg/l)} - 4.32
\]

A value below 90 ml/min/1.73 m² was considered a criterion for reducing GFR [19].

Urine TGF-β1 levels were measured once during the first month of the study. The TGF-β1 ELISA kit (DRG International, Inc., USA) was used to measure the TGF-β1 marker. The DRG TGF-β1 ELISA kit is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle. Urine samples for the determination of TGF-β1 were collected once (morning urine). Urine was stored at –80 °C prior to analysis. Samples were thawed prior to enzyme-linked immunosorbent assay.
Design of the study

A cross-sectional study

I stage

The formation of groups of examinees with the study of clinical and anamnestic data
Examination of patients using standard nephrological methods
Examination of patients using kidney biomarkers (serum cystatin C, TGF-β1 in urine)

II stage

Statistical processing of the obtained data and statistical analysis were performed using the STATISTICA 6.1 software package.
Determination of the characteristics of comorbid kidney damage in children with JIA, taking into account the indicators of renal biomarkers.
Determination of risk factors for functional and structural kidney damage in children with JIA.

The χ² test and Fisher’s exact test were used as statistical methods for the study of the TGF-β1 correlation tables. All obtained results were accepted as statistically probable with a symptomatic significance of less than 0.05 (p<0.05). To quantify the significant association between TGF-β1 and the outcome variables, odds ratios (OR) with confidence intervals of the 95 % range (CI) were calculated. The odds ratio helps identify how likely an exposure is to lead to a specific event [3]. The diagnostic determination of the odds ratio allows you to objectively assess the productivity of the diagnostic determination performed for the disease being studied.

Odds Ratio = (odds of the event in the exposed group) / (odds of the event in the non-exposed group)

Descriptive statistics of interval variables were described as mean, standard deviation, median, upper and lower quartiles. Spearman’s rank correlation was used to determine the degree of association between TGF-β1 concentration and other interval data. Statistical analysis was performed using the software package STATISTICA 6.1® (StatSoft Inc., serial number AGAR909E415822FA).

The work was carried out as part of the research work of the Department of Propaedeutic of Childhood Diseases and Pediatrics 2 of the Dnipro State Medical University «Development of criteria for early diagnosis and prediction of comorbid kidney damage in children with somatic and infectious diseases» (state registration No. 0119U100932, implementation period 01.2019-12.2023).

The results of the data obtained and their discussion

We examined 80 children with JIA, including 46 (57.5 %) girls and 34 (42.5 %) boys. The age of the subjects was 10.4 ± 4.41 (10.6-15.0) years. The debut of JIA was observed at the age of 5.8 ±4.14 (4.9; 2.9) years. The following variants of the clinical course of JIA were noted: systemic arthritis – 9 (11.3 %), polyarthritis – 47 (58.8 %), oligoarthritis – 24 (30.0 %) cases. Remission of JIA was diagnosed in 60 (75.0 %) children, low JIA activity – in 14 (17.5 %), high JIA activity – in 6 (7.5 %).

When patients were examined for kidney damage using standard methods, no pathological changes in the general urine analysis, creatinine and urea, GFR by the Schwartz formula, or kidney sonography.

The mean urinary TGF-β1 level was 20.26±16.34 (14.02, 12.5-17.98) pg/ml. Based on the fact that there are currently no standardized normative data on urinary TGF-β1 levels in children, we formed a sample of patients who had a TGF-β1 level not less than the upper quartile of the variation series we studied (17.98 pg/ml) and conducted a comparative analysis with a sample of patients with a TGF-β1 level <17.98 pg/ml. Factor tables of frequency distribution of clinical course, comorbidities, and therapeutic regimens of JIA depending on the urinary TGF-β1 level were investigated. Based on the results of this analysis, factors significantly associated with elevation TGF-β1 levels were identified and are shown in Table 1.
According to the data obtained, male gender reduced the risk of elevated TGF-β1 sixfold (Table 1). Among children with elevation TGF-β1, boys were 3.4 times less common than in the sample with TGF-β1 below 17.98 pg/mL, p<0.005. Polyarthritis almost quadrupled the chances of pathological changes in TGF-β1. The overwhelming majority of children with elevation TGF-β1 suffered from polyarthritis (80.0 %) – one and a half times more often than those with a relatively normal TGF-β1 concentration, p<0.04.

The mean duration of JIA was 4.6±3.03 (4; 2.58-6) years, and in 22 (27.5 %) cases it was at least 6 years, twice as often in the background of elevated TGF-β1, p<0.05. With this duration of JIA, the risk of TGF-β1 hyperproduction increased almost threefold. The duration of the active phase of JIA was 3.0±2.28 (2.3; 1.5-4) years, and in 22 (27.5 %) cases it was at least 6 years, and in 22 (27.5 %) cases it was at least 6 years, twice as frequent in children with elevated TGF-β1, p<0.04. The presence of caries increased the odds of to elevation TGF-β1 levels and more than six times increased the odds of to elevation TGF-β1. One of the markers of JIA activity is ESR. Patients with elevated TGF-β1 were three times more likely to have an ESR above normal than children with TGF-β1<17.98 pg/mL, p<0.02. The presence of a high ESR more than quadrupled the risk of elevated TGF-β1. In addition, TGF-β1 was positively correlated not only with ESR (ρ=0.38, p<0.001) and urine TGF-β1 marker almost as much as polyarthritis (Table 1).

In 8 (10.0 %) of our patients were diagnosed with hypertension. This pathology is both a cause and a consequence of CKD [20], was five times more likely to be associated with high TGF-β1 levels and more than six times increased the odds of to elevation TGF-β1. One of the markers of JIA activity is ESR. Patients with elevated TGF-β1 were three times more likely to have an ESR above normal than children with TGF-β1<17.98 pg/mL, p<0.02. The presence of a high ESR more than quadrupled the risk of elevated TGF-β1. In addition, TGF-β1 was positively correlated not only with ESR (p=0.35, p<0.002), but also with neutrophil count (p=0.38, p<0.001) and urine pH (p=0.23, p<0.05). It was inversely correlated with lymphocyte count (p=0.40, p<0.001).

Since there were no changes in TGF-β1 levels as a function of creatinine and GFR calculated by the Schwartz formula in our study, we performed a more detailed analysis of renal functional status, including cystatin C and GFR calculated by the Hoek formula based on cystatin C, and examined their relationship with TGF-β1 concentration. According to Hoek GFR, 33 (41.3 %) patients with JIA had renal dysfunction. On the background of elevated TGF-β1, a reduced GFR according to the Hoek formula (< 90 ml/min/1.73 m2) was found in 95 % of cases, i.e. the estimates of the functional state of the kidneys obtained by two different methods were quite clearly the same. The adequacy of these methods was also demonstrated by the excessive OR value for the correlation of TGF-β1 with GFR (Table 1) and their close inverse correlation (p=–0.88, p<0.001).

From the results of the analysis, it can be concluded that the highest diagnostic value in the examination of patients with JIA is the calculated value of glomerular filtration measured by cystatin C and not by creatinine, which is consistent with the results of the study. [21].

The central issue in JIA is the question of therapy. Treatment should be proactive, aggressive and as effective as possible. To reduce the manifestations of the joint...
syndrome, the first line of treatment is the use of NSAIDs. The drugs are prescribed individually and for varying periods of time – until a clinical effect is achieved. At the time of our study, 22 (27.5%) children were taking NSAIDs. The mean duration of their use for the entire duration of JIA was 4.6±4.91 (3; 2-6) years. All patients were also receiving methotrexate. The use of NSAIDs was 2.5 times more likely to be associated with elevation of TGF-β1 (p<0.02) and quadrupled the odds of its elevation. Our data are consistent with the results of the study by Glicchin MF et al [9], according to which the main risk factor for CKD in children with JIA is prolonged exposure to NSAIDs and methotrexate in active forms of the disease.

In our study, immunobiologic therapy was used in 25 (31.3%) cases for a mean of 3.0±2.23 (2.3; 1.4-4.3) years. In the sample with TGF-β1<17.98 pg/ml every third to fourth child received it, in the sample with elevated TGF-β1 only every tenth child. Immunobiologic therapy reduced the risk of increasing this marker in urine by 5.5 times.

In summary, the above results are consistent with the conclusion of Tang PC et al. that short-term activation of TGF-β1 promotes renal recovery and prolonged activation of this growth factor causes fibrosis and progression of CKD [22]. The role of TGF-β1 in the pathogenesis of renal nephrosclerosis, which is associated with the development and progression of CKD, should not be underestimated [23].

Conclusions

1. An elevated level of the TGF-β1 biomarker was found in 25% of children with JIA.
2. An association of early kidney fibrosis with the duration of the active stage of JIA ≥4 years (OR=6.11; CI: 2.01-18.58; p<0.01), an increase in ESR (OR = 4.33; CI: 1.35-13.88; p<0.05), polyarthritis (OR=3.74; CI: 1.12-12.51; p<0.05), arterial hypertension (OR=6.33; CI: 1.36-29.55; p<0.05), caries (OR=3.24; CI: 1.14-9.22; p<0.05).
3. The male gender significantly reduces the risk of early kidney fibrosis – almost to the same extent as this risk is increased by hypertension and a long active stage of JIA.
4. Increased level of TGF-β1 in urine is associated with reduced GFR (OR=15.58; CI: 4.02-60.36; p<0.001) and is observed in almost all children with GFR<90 ml/min/1.73 m², which confirms the importance of early fibrosis of the kidneys in the development of kidney dysfunction.

Prospects for further research. To build a multifactorial regression model for predicting comorbid kidney damage in children with JIA.

Conflict of Interest. The authors declare no conflict of interest.

Source of Funding. This work received no external funding.

References:


ФАКТОРЫ РИЗИКА ТА КЛІНІЧНІ КОРЕЛЯЦІЇ TGF-β1 В СЕЧІ У ДІТЕЙ З ІДІОПАТИЧНИМ ІДІОПАТИЧНИМ АРТРИТОМ ТА РАНИМ ФІБРОЗОМ НИРОК

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Резюме.

Вступ. Перебіг ювінельного ідіопатичного артриту (ЮІА) пов'язаний із тривалим запальним процесом та застосуванням нестероїдних противозапальних засобів, які потенційно можуть спричинити нефротоксичний ефект зібрання ураження нирок у хворих на ЮІА. Незалежно від етiологiчного суттєвого ускладнення тривала запалення сприяє прогресуванню фіброзу, а фіброз нирок є кінцевою стадією хронічної хвороби нирок (ХХН). Біосія нирки, яка є інвазивним і ризикованим методом і не використовується регулярно вважається єдиним клінічним інструментом для виявлення фіброзу. Разом з тим, за останні десятиліття було досягнено певного прогресу в пошуку мінімально інвазивних біомаркерів раннього фіброзу нирок, причому ключова роль у прогресуванні фіброзу нирок відводиться трансформуючому фактору росту-β1 (TGF-β1), однак не відомі значення TGF-β1 у дітей, хворих на ЮІА.

Мета дослідження – визначити взаємозв'язок рівня TGF-β1 у сечі, як меркера раннього фіброзу нирок у дітей, хворих на ЮІА, залежно від клінічного перебігу захворювання, особливостей коморбідних факторів та схем лікування.

Матеріал і методи дослідження. Обстежено 80 дітей з ЮІА. Рівень TGF-β1 у сечі визначали за допомогою набору TGF-β1 ELISA (DRG International, Inc., Німеччина, EIA-1864) відповідно до інструкцій виробника.

Для всіх пацієнтів отримано інформоване згоду. Дослідження має позитивний висновок комісії з питань біомедичної етики Дніпровського державного медичного університету (протокол засідання комісії № 12 від 19.12.2023 року), яка постановила, що наукове дослідження вважати таким, що відповідає загальнодержавним нормам моралі, вимогам дотримання прав, інтересів та особистої доцільності учасників дослідження, біосетевим нормам роботи з хворими дитячого віку. Ризик для суб'єктів дослідження під час виконання роботи відсутній. Законних представників дітей, які залишили до дослідження, інформують про всі аспекти, пов'язані з метою, задачами, методиками та очікуваною користю дослідження.

Лабораторні та інструментальні методи дослідження є загальнодержавними, препарати, що будуть використани, дозволені до застосування. Експерименти на людині не проводились.

Використовували методи варіаційної статистики. Статистичний аналіз виконували за допомогою програмного пакету STATISTICA 6.1® (StatSoftInc., серійний № AGAR0909415822FA). Робота виконана в рамках науково-дослідної роботи кафедри пропедевтики дитячих хвороб та педіатрії 2 Дніпровського державного медичного університету (розробка інтерпретації інформації, прогнозування коморбідного ураження нирок у дітей з соматичними та інфекційними захворюваннями) (державний реєстраційний № 0119U100836, термін виконання 01.2019-12.2023 рр). Результати дослідження. Середній вміст TGF-β1 у нашому дослідження становив 20,26±16,34 (14,02; 12,5-17,98) пг/мл. Поларпарт майже в чотири рази більша шанс включення рівня TGF-β1. Стандартизованих нормативних даних щодо рівня TGF-β1 в сечі у дітей на даній момент відсутні, ми сформували вибірку пацієнтів, які мали рівень TGF-β1 не нижче верхнього кварталу досліджуваного нами варіаційного ряду (17,98 пг/мл) і проведіли порівняльний аналіз із вибіркою пацієнтів із рівнем TGF-β1 >17,98 пг/мл. Переважна більшість дітей у підінічнені TGF-β1 хворіли на поларпарт (80,0 %) – у півтора рази частіше, ніж із відносно нормальною концентрацією TGF-β1, p<0,04.

Якщо активна стадія захворювання тривала понаднечатки роки, шанси на підвищення TGF-β1 зросли більш ніж у шість разів. Тенденцію значної нефротоксичного ефекту інфузії активного ЮОА підтверджено результатами корелюваної аналізізу, згідно з яким, в цілому, тривалість активного ЮОА безпосередньо пов’язана зі збільшенням TGF-β1 (r=0,38, p=0,001), а тривалість ремісії та загальна тривалість ЮОА достовірно не корелювали з нею (відповідно r= –0,19 та p=0,18, r=0,05).
Встановлено пряму залежність підвищення рівня TGF-β1 у сечі від клінічних проявів поліартриту та тривалості активної стадії ЮІА. Ці клінічні ознаки у дітей з ЮІА можна розглядати як фактори ризику розвитку раннього фіброзу нирок. На тлі підвищення TGF-β1 у 95 % випадків виявлено знижену розрахункову швидкість клубочкової фільтрації (РШКФ) за формулою Ное (т <90 мл/хв./1,73 м²), тобто оцінки функціонального стану нирок, отримані за двома різними методами були цілком одноznachними. У вибірці з TGF-β1 >17,98 пг/мл – 22,76 % дітей отримували імунобіологічну терапію, тоді як у вибірці з підвищення TGF-β1 – лише 14,76 %. Імунобіологічна терапія знижала ризик підвищення цього сечового маркера в 5,5 разів.

Висновки. Підвищення рівень біомаркеру TGF-β1 виявлено у 25 % дітей з ЮІА. Встановлена асоціація раннього фіброзу нирок з тривалістю активної стадії ЮІА>4 років, підвищеним ШОЕ, поліартритом, артеріальною гіпертензією, карієсом зубів. Чоловіча статя значче знижує ризик раннього фіброзу нирок – практично в такому же ступні, як цей ризик підвищують АГ і тривала активна стадія ЮІА. Підвищений рівень TGF-β1 в сечі асоціюється зі зниженою РШКФ та відмічається практично у всіх дітей зі рШКФ<90 мл/хв./1,73 м², що підтверджує значення раннього фіброзу нирок в розвитку ниркової дисфункції.

Ключові слова: ювенільний ідіопатичний артрит; нирки; діти; маркер фіброзу; TGF-β1; імунобіологічна терапія; ураження нирок.

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Received for editorial ofce on 23/12/2023
Signed for printing on 10/02/2024